hydroxide followed by relactonization, protecting the hydroxyl group on the lactone ring, then acylation with 2,2-dialkylbutyryl acid and deprotecting the lactone hydroxyl group.

Taoka et al is relied upon to teach an analogous process which uses lithium hydroxide or potassium hydroxide in a 1 to 10 ratio based on lovastatin with 2,2dimethylbutyryl chloride as the acylating agent. The Office Action refers to the disclosure at column 2 lines 1-65, column 3 lines 25-30, column 4 lines 40-46, and column 5 lines 33-36.

Dabora et al is relied upon to teach an analogous process for acylating using 2,2dimethylbutyryl acid or the 2,2dimethylbutyryl chloride derived therefrom. The Office Action refers to the disclosure at column 2 lines 5-15 and column 4 step c.

The Office Action states that Hoffman et al differs from the claimed invention that the former uses lithium hydroxide instead of potassium hydroxide, and a dialkylbutyryl acid instead of a dialkylbutyryl bromide or chloride.

Applicants respectfully disagree with the Office Action's understanding of the references and the claimed invention and traverse it for the following reasons.

The present invention is clearly not obvious over Hoffman et al. taken with Taoka et al. in view of Dabora et al., for the reason that **the inventive method is different from the processes of the cited references in terms of the catalyst used in the hydrolysis step (a) and the acylation step (c) in claim 1**.

The following table summarizes the catalysts used in the process of the present application, Hoffman et al, Taoka et al, and Dabora et al. The table clearly shows that the combination of the references does not lead to the claimed invention.

	Catalyst used in Hydrolysis step (a)	Catalyst used in Acylation step (c)
Claim 1 of Present Application	a mixture of potassium hydroxide **methanol(primary alcohol)-water: a ternary system**	quaternary ammonium halides or quaternary phosphonium halides
Hoffman et al	lithium hydroxide	4-dimethylaminopyridine
Taoka et al	a mixture of potassium hydroxide **secondary or tertiary alcohol: a binary system**	4-dimethylaminopyridine
Dabora et al	-	-

i) Hydrolysis step (a)

In the inventive method defined in claim 1, the hydrolysis step (a) is performed using **a mixture of potassium hydroxide-methanol(primary alcohol)-water (a ternary system)**.

In this regard, Examiner has pointed out that Hoffman et al. use lithium hydroxide instead of potassium hydroxide in the hydrolysis step unlike the present invention, but the use of potassium hydroxide in an analogous process is taught by Taoka et al.

However, as set forth above, it should be noted that although the use of potassium hydroxide is disclosed in Taoka et al. as the Examiner pointed out, the method of Taoka et al. differs from that of the present invention in that **it uses a binary system, i.e., a mixture of**

potassium hydroxide and a secondary or tertiary alcohol such as butyl alcohol, while the present invention employs a ternary system involving a primary alcohol.

In this regard, the Office Action mentions that the use of methanol would have been obvious over the teaching of ethanol (*see* page 3, lines 15 and 16 of the Office Action). However, Applicant submit that none of the references teach a ternary system involving ethanol or other types of alcohol in the hydrolysis step of a process of preparing simvastatin from lovastatin.

Furthermore, as the Examiner has pointed out, the method of Hoffman et al. involves a hydrolysis step (a) **using only lithium hydroxide** (*see* column 13, line 60 of Hoffman et al.), and Hoffman et al. do not disclose or teach a hydrolysis step employing a mixture of potassium hydroxide-methanol-water.

As the result of such difference, **the hydrolysis step according to the present invention produces a higher yield and purity of the product and is performed in different reaction conditions from those of Hoffman et al. and Taoka et al.**

Specifically, the hydrolysis step according to the **inventive method** may be performed at **a mild temperature for a short period of time (e. g, 20 °C for 8 hours) to give a product of a higher purity (e.g., 98.6% or higher), in a high yield (e.g., about 98%)** (see page 9. lines 10 to 19 of the specification).

In contrast, the method of Hoffman et al. requires **a high temperature and a long reaction time of 56 hours for the hydrolysis procedure**, which leads to a number of undesired by-products, **causing a low yield of about 83% and a low purity of the final product** (*see*

column, 13 line 60, and Examples 2 and 5 of Hoffman et al.), which is markedly lower than that achievable by the present invention.

Further, the triol acid obtained by the hydrolysis step according to the Taoka et al. is obtained as a **brown-colored oil** (*see* column 4, lines 16 to 18 and column 6, lines 49 and 50 of the Taoka et al.), which indicates that the **product obtained by Taoka et al contains a high content of undesirable by-products**.

As described above, the much improved, desirable effect obtained by using the hydrolysis step of the present invention can not be achieved by the methods of Hoffman et al. and Taoka et al., and, thus, the hydrolysis condition of the present invention cannot be easily conceived even when Hoffman et al and Taoka et al. are combined.

ii) Acylation step (c)

In the inventive method defined in claim 1, **the acylation step (c) is carried out in the presence of a quaternary ammonium halide (compound of formula (VII)) or quaternary phosphonium halide (compound of formula (VIII)) as an acylation catalyst** which facilitates the completion of the reaction, shortening the process time,

In this regard, Examiner has pointed out that the method of Hoffman et al. uses a tetrabutylammonium fluoride instead of tetrabutylammonium bromide used in the present invention as an acylation catalyst, and Dabora et al. also teach an analogous acylation process that uses 2,2-dimethylbutyryl acid or the 2,2dimethylbutyryl chloride derived therefrom.

However, **tetrabutylammonium fluoride** used in Hoffman et al. **is used not as an acylation catalyst** but as an agent to facilitate the deprotection of tertbutyldimethylsilyl (TBDMS) in a deprotection step (*see* column 14, lines 3 and 4 of Hoffman et al.), and **the acylation catalyst used in Hoffman et al. is 4-dimethylaminopyridine** (see column 14, lines 19 to 23 of Hoffman et al).

Further, in the method of Dabora at al., the acylation step (c) is carried out using 2,2-dimethylbutyryl acid or the 2,2-dimethylbutyryl chloride **in the absence of an acylation catalyst** (*see* column 3, lines 23 to 27 of Dabora et al.), and Taoka et al. also disclose **an acylation step (c) using 4-dimethylaminopyridine** as an acylation catalyst, as Hoffman et al do.

Thus, the use of a specific catalyst, a quaternary ammonium halide or quaternary phosphonium halide in the acylation step (3), is not taught, suggested or implied by Hoffman et al., Taoka et al. or Dabora et al.

In this regard, in order to demonstrate the beneficial effect of using the acylation catalyst of the present invention, the applicant conducted experiments to compare the catalytic effects brought about by the use of a quaternary ammonium halide or quaternary phosphonium halide of the present invention and 4dimethylaminopyridine used by Hoffman et al. and Taoka et al., and results are attached hereto in the form of 37 C.F.R § 1.132 declaration.

As demonstrated in the declaration, **the compound of formula (VI)** prepared in accordance with **the inventive acylation condition** is obtained in a **high yield of 98% or**

higher. In contrast, **in case that the acylation step (c) is carried out in the presence of 4-dimethylaminopyridine** as an acylation catalyst as disclosed in Hoffman et al. and Taoka et al., the compound of formula (VI), is obtained **in a yield of about 75%**, which is markedly lower than that of the present invention.

As the result of such difference effects of acylation catalysts examined, the final product, **simvastatin, having a high purity can be obtained in a high yield according to the present invention** (see Example 5 of the present invention).

In this regard, the Examiner pointed out that the Applicant's comments based on yields and purities are not persuasive since they are not recited in claims (see page 3, lines 13 to 15 of the Office Action). However, we strongly believe that the high yield and purity of the final product is the effect of the subject invention rendered by the constitutional differences as indicated above, and it is not necessary to describe the effect of the invention in the claims.

Accordingly, it is believed that the constitutional features and effects of the present invention are not obvious over Hoffman et al. taken with Taoke et al. in view of Dabora et al., and, therefore, the rejection cannot be sustainable. It is respectfully requested that the rejection be withdrawn.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the

Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

/Sunhee Lee/

Sunhee Lee
Registration No. 53,892

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

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